Grant# MH68036

Center Director: Zachary N. Stowe, M.D.

Center Overview

This is an application for RFA-OD-02-002 to fund a Specialized Center of Research on Sex and Gender Factors Affecting Women's Health representing the collaborative efforts of five departments and two academic institutions. The central theme of the application is "pharmacokinetic, pharmacodynamic, and pharmacogenetic (PK/PD/PG) modeling of anti-epileptic drugs (AED) and psychotropic medications during pregnancy and lactation using both human and rodent paradigms: defining fetal/neonatal exposure and influence on obstetrical outcome". The primary objectives of the center include: 1) PK/PD/PG modeling of anti-epileptic drugs (AED) and psychotropic medications antidepressants, lithium) during pregnancy and lactation. These novel data will provide information about the metabolism, distribution, and extent of fetal/neonatal exposure to these medications. The data for this modeling will be obtained from women with neurological disorders (Epilepsy, Tourette's Syndrome) and mental illness (Bipolar Disorder, Major Depression, Obsessive Compulsive Disorder, Panic Disorder). These patient populations were selected based on the typical chronic course of illness and utilization of similar medications between the groups. The PK/PD modeling from subjects with different illnesses and ethnic groups enhances the pharmacogenetic (PG) comparison of metabolic capacity and protein binding. 2) These clinical data will be complemented by a series of laboratory animal studies in two strains of rodent (one deficient in 2D6 activity) to provide fetal and neonatal central nervous system (CNS) tissue concentrations, neonatal CNS clearance, and neurotransmitter receptor effects of antenatal and postnatal exposure to AEDs and psychotropic medications. 3) Prospective assessment of these women will provide documentation of all additional exposures (prescription medications, over the counter preparations, herbal remedies, maternal illness events, environmental toxins) and delineation of the course of illness during pregnancy and postpartum. The ultimate clinical import of these data will be clarification of the factors influencing medication metabolism and distribution, thereby providing an estimate fetal/neonatal exposure, factors influencing such exposure, and novel data regarding the potential "dose versus outcome" comparison. The multidisciplinary team of this center application represent two academic medical centers and five departments organized into 2 clinical projects, 1 laboratory investigation, supported by 3 core components and an executive committee with extensive research/clinical experience. The achievement of the objectives address several research priority areas noted in ORWH Agenda for Research on Women's Health for the 21st century.

Principal Investigator: Page Pennell, M.D.

Project 1: Epilepsy and Childbirth: PK/PD Modeling of AEDs

Approximately 1.1 million women with epilepsy are of childbearing age in the United States and give birth to over 20,000 babies each year. Pregnancy in women with epilepsy is accompanied by increased adverse neonatal outcomes, and approximately 28% of women will experience increased seizures. Serum concentrations of most of the AEDs decline during pregnancy, but findings from previous studies are too inconsistent to provide guidelines for management of AEDs during pregnancy. The primary objectives of Project 1 are: 1) pharmacokinetic/pharmacodynamic (PK/PD) modeling of antiepileptic drugs (AEDs) during pregnancy and lactation in women with epilepsy to define fetal/neonatal exposure; 2) identifying the predictors of seizure worsening during pregnancy and postpartum. Given that both AEDs and maternal seizures have been identified as having deleterious effects on the developing fetus and neonate, the PK/PD modeling combined with the course and predictors of illness will provide the foundation to propose guidelines to reduce exposure to both seizure activity and medication. PK/PD modeling of each of the AEDs encountered will be performed in Core A. Both a traditional, two-stage approach and population PK modeling will be employed. The influence of gestational age and other demographic, genetic, and environmental factors (covariates) will be analyzed. Frequency of seizures by type will be documented throughout pregnancy and first postpartum year and compared to each woman's preconception baseline. Worsening of seizure frequency will be correlated with potential predictors, including change in serum AED concentrations, hormonal status, stress, and altered sleep patterns.

Principal Investigator: Zachary N. Stowe, M.D.

Project 2: Mood and Anxiety Disorders in Pregnancy and Lactation

The treatment of mental illness during pregnancy has gained considerable attention over the past decade. The majority of this attention has focused on antidepressants and major depression, with far less consideration of anxiety disorders and bipolar disorder. The treatment guidelines for mental illness during pregnancy and lactation remain empiric and continue to emphasize the risk/benefit assessment. The lack of data on the course of illness, the impact of pregnancy and lactation of the metabolism and distribution of pharmacological treatments, and the extent of fetal and neonatal medication exposure underscores the empiric nature and prematurity of such guidelines. The current project will enhance and extend the data derived from an ongoing collaborative R01 MH56555-01A2 (Stowe) focused on the relapse of major depression in pregnant women taking antidepressant proximate to conception and K23 MH 63507-01 (Newport) investigating psychosis during pregnancy. We will prospectively follow women with major depression (MID), bipolar disorder (BPD), panic disorder (PD), and obsessive-compulsive disorder (OCD) through pregnancy and the first postpartum year. Many of these women may chose to continue medications such as antidepressants, mood stabilizers, and antipsychotic medications either during pregnancy and/or take medications postpartum. Monthly serum sampling and GCRC admissions will provide novel data regarding the metabolism, distribution, and fetal/neonatal exposure to these compounds. These PK/PD models will be expanded to include assessment of pharmacogenetic factors of metabolic capacity and protein binding. Similarly, prospective documentation of additional exposures, sex steroid concentrations, and psychosocial variables will further refine such models and provide preliminary assessment of factors (other than medication concentrations) that may influence the course of illness and obstetrical outcome. The current project will utilize the core components to address the deficits in the current literature, affords a diagnostically diverse group of women that may be germane to the results obtained in Project 2 with respect to co-morbidity and the use of similar medications in a non-epileptic population.

Principal Investigator: Michael J. Owens, M.D.

Project 3: AEDs and Psychotropics in Pregnancy: Rodent Model

The management of mental and neurological illnesses during pregnancy and lactation raises complex clinical issues. There have been vast changes in the pharmacological armamentarium available to these disorders, but clinical reproductive safety data regarding these compounds is limited and slow to accumulate due to the ethical and logistical complexities of conducting such clinical research. Furthermore, peripheral measures of neurotropic medication concentrations (e.g. infant serum, breast milk) may not reflect the magnitude of fetal or neonatal central nervous system (CNS) exposure to these compounds. In this context, laboratory animal models present an invaluable means to study the developmental impact of CNS exposure to neurotropic medication. Using a rodent model, this project quantifies offspring CNS exposure by measuring the brain concentrations of numerous neurotropic medications delivered during pregnancy or lactation and assessing the rate of offspring clearance of these medications after delivery. In addition, this project assesses the functional impact of CNS exposure by measuring alterations, if any, in the density and regional distribution of medication-specific neurotransmitter receptors and transporters that are associated with drug administration. The project also models the impact of genetic polymorphism of hepatic microsomal enzymes upon offspring CNS exposure by duplicating the experiments in a rodent strain genetically deficient of a hepatic isoenzyme. Finally, this project contributes a clear translational component to the overall SCOR by utilizing commonly prescribed medications for the treatment of neurological and psychiatric conditions during pregnancy. Further, this project will be responsive to the clinical experience of the other projects, e.g. should a new medication that is not included in the present application emerge as a primary treatment modality, methodology will be rapidly developed to obtain CNS exposure data.

Principal Investigator: Lindsey C. Devane, Ph.D.

Core: PK/PD/PG Modeling

The Pharmacokinetics/Pharmacodynamics (PK/PD) Core (Core A) provides mathematical modeling of data collected in the three major projects. Core A contributes to the objectives of the SCOR by providing both data analysis and patient specific pharmacogenetic data to develop and test models describing the dose/ concentration-effect relationships of antidepressants (AD) and antiepileptic drugs (AED) used during pregnancy. For most drugs, pharmacokinetic and pharmacodynamic information is or at least should be the scientific basis for their clinical use. In pregnancy, the dynamic physiological changes that occur in the maternal/placental/fetal unit influence the processes of drug absorption, distribution and elimination leading to varying drug dosage requirements and uncertainty about the extent and consequences of fetal drug exposure. Through population pharmacokinetic modeling, we will identify sources of inter and intra-individual variability in the concentration/time course of AD and AED from the administration of a certain dose. Fetal drug exposure will be predicted using maternal/umbilical cord concentrations obtained at birth. Covariables will be identified and rank ordered for importance that influence this exposure. A variety of effect measures corresponding to the primary disorder for which the AD and AED are being administered will be incorporated into the modeling process. These data analyses in Projects 1 & 2 will be complemented by animal experiments in Project 3 in which access to tissue drug concentrations unavailable in humans should allow further insight into factors influencing fetal drug exposure. Core A will apply the three major categories of pharmacokinetic models, compartmental, physiological and statistical, along with direct and indirect pharmacodynamic models, to explain and predict the role of maternal drug exposure to health and pregnancy outcomes.

Principal Investigator: James C. Ritchie, Ph.D.

Core: Assay

The purpose of this Core is to provide a common set of state-of-the-art biochemical analyses to Center researchers. The Core laboratory will provide assessments of hypothalamic/pituitary/adrenal axis function, reproductive axis function, antidepressant and antiepileptic drug concentrations to the individual Research Projects of the Center. Accurate measurement of these parameters is imperative to fully characterize each of the clinical model systems of pregnancy (i.e. pregnancy with major depression, pregnancy with epilepsy, pregnancy with bipolar disorder, etc) being investigated by the Center. Accurate determination of drug concentrations (and their metabolites) is also central to the development of PK/PD models and the preclinical investigations being conducted by Center investigators. Having these determinations performed by a central facility using a common set of assay modalities will provide an unprecedented opportunity to compare these models and preclinical investigations with direct clinical data. Additionally, having a Core devoted to these analyses will guarantee high quality assay performance, allow for economies-of-scale in the purchase of assay reagents and technician time, and enable Center investigators to more fully concentrate their efforts on the unique aspects of their particular project.